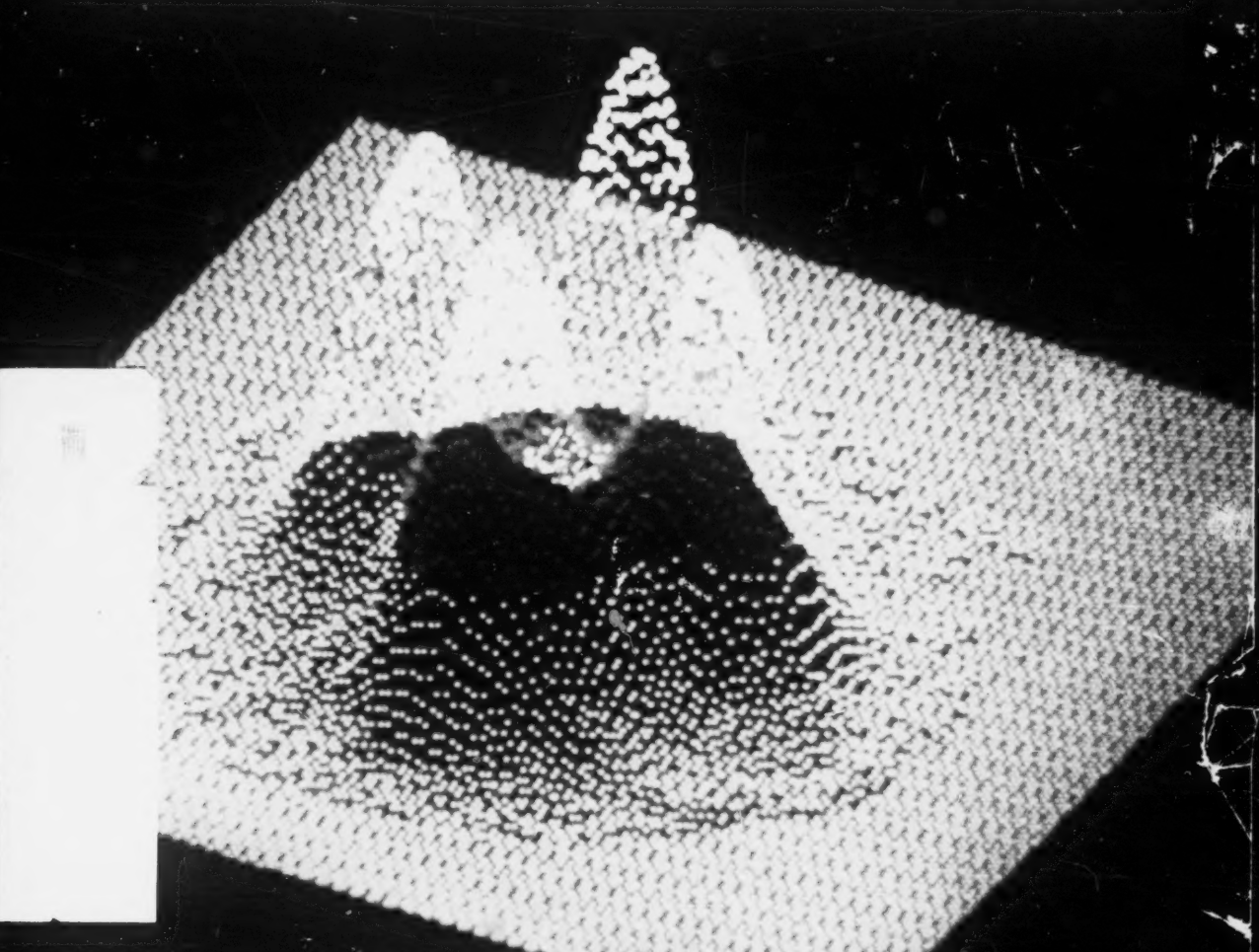


CHEMICAL & ENGINEERING NEWS

C&EN

MARCH 29, 1991

BIOTECH FIRMS FINANCIALLY STRONG DESPITE LOSSES IN 1991 PAGE 9



SURFACE CHEMISTRY

Rich connections to technology Page 22

**NEWS
OF THE WEEK**

■ Bolstering of federal support for precommercial R&D—the work occurring after basic research and before prototype creation—is urged in report issued last week. **Page 4**

■ Australian effort to streamline text for global chemical weapons treaty is welcomed by participants in negotiations and may considerably shorten time for approval of final document. **Page 5**

■ NIH director Bernadine Healy charges that leaks of confidential documents from the agency's scientific misconduct office endanger NIH. **Page 5**

■ John Sheehan, organic chemist renowned for being the first to perform a total synthesis of a penicillin, dies at age 76. **Page 6**

■ BASF Corp. agrees to sell its U.S. rayon fiber operations to Austria's Lenzing; firm also announces closing of plant in California. **Page 6**

COVER: Measurement of the chemical bond direction for adsorbed chlorine on the Si(100) surface produces this digital electron stimulated desorption ion angular distribution (ESDIAD) pattern. The image was generated by the Surface Science Center, Department of Chemistry, University of Pittsburgh.

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BUSINESS

Biotech companies currently are flush with cash for R&D funding despite heavy losses in 1991 for many of them, primarily because of lucrative public stock offerings. **Page 9**

GOVERNMENT

House subcommittee criticizes as inadequate an EPA environmental equity report aimed at determining how the agency has responded to high environmental risks borne by the poor and minorities. **Page 13**

SCIENCE/TECHNOLOGY

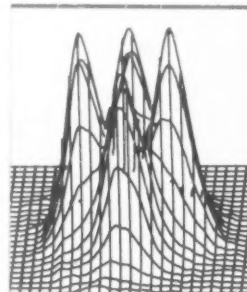
Amoco's new process for making polypropylene and ethylene/propylene copolymers features a unique reactor design and a high-activity catalyst. **Page 17**

Survey of U.S. undergraduate biochemistry departments by North Carolina State University shows that the University of California, Davis, is the largest, with 575 students. **Page 18**

ACS NEWS

ACS publications choose advisory board members; two new developments in ACS elections; society's News Service initiates series of news briefings for science journalists. **Page 19**

**SPECIAL
REPORT**



The synergism of fundamental and applied research in surface chemistry has fueled a better understanding of the basic and applied activities of technologies such as heterogeneous catalysis, semiconductor processing, new materials development, and analytical techniques. **Page 22**

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LETTERS

CHEMICAL SAFETY

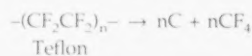
Perfluorocarbon flammability

You have published a number of letters on perfluorocarbon flammability. All of these tried to correct possible misconceptions in the minds of the readers about perfluorocarbon inertness. The latest letter by Eric R. Larsen (C&EN, Feb. 17, page 2) gives a fine discussion on the elements necessary for flammability. His reference [Larsen's own publication, *Fluorine Chemistry Reviews*, 3, 24 (1969)] is well worth reading for those interested in flammability of halogenated compounds. However, it would be incorrect to infer from Larsen's letter that the table of flammability limits includes many perfluorocarbons. In fact, there are only seven: two are the highly reactive aromatic compounds, perfluorotoluene and perfluorobenzene; three are cyclic compounds of lower stability than straight chain compounds; one is perfluorobutane, where the lower flammability limit in pure oxygen is given as "<50%"; and the last is hexafluoroethane, which does not have a lower flammability limit. Clearly, a generalization on the flammability of perfluorocarbons cannot be drawn from this group.

I believe there are three additional points to be made on this subject. First, the name perfluorocarbon, whatever the original intention was, has come to apply to organic compounds

where the only element attached to carbon (other than another carbon) is fluorine. This means that the toluene with all the hydrogens replaced by fluorine is commonly called perfluorotoluene. This compound is a highly reactive compound because of the unsaturation in the ring, and it should be no surprise that it reacts violently with high-pressure oxygen (C&EN, Sept. 23, 1991, page 2). It would be wiser to restrict the perfluorocarbon name to fully saturated inert fluoro-organic compounds.

Second, the ultimate reaction of any organic compound with oxygen at extreme temperatures and pressures is also not surprising (C&EN, Oct. 7, 1991, page 2). In fact, neither oxygen nor other aggressive chemicals are needed at all for doomsday predictions with perfluorocarbons. Consider the following:



This reaction is exothermic to the extent of 29 kcal per mole, but, of course, the energy of activation is extremely high.

Third, a blanket assumption of inertness without examining all the data is unwise.

Louis I. Ferstandig

Vice President and Technical Director
Halocarbon Products Corp.
River Edge, N.J.

Undergraduate curricula

In Peter Lykos' letter (C&EN, Jan. 27, page 3), he has placed one of the central questions about undergraduate chemistry curricula on the table: What constitutes an introduction to our discipline, and why do we persist in offering up the cart before the horse in the form of general chemistry courses based on "baby p. chem"? Lykos suggests that a better representation of chemistry is the more qualitative model used by organic and inorganic chemists, which uses the language of chemistry and reasoning by analogy to describe observable, macroscopic changes in reactivity in terms of microscopic

chemical structure. I am pleased to provide some observations from a curricular experiment based on exactly these principles, which began in September 1989 at the University of Michigan.

Last fall, using their performance on a 40-question ACS high school examination as a guide, 975 out of the 2500 students taking an introductory chemistry course at Michigan chose to start in a course titled, "Structure and Reactivity." The two-term course uses mechanistic organic chemistry as the primary context for illustrating the how and why of scientific inquiry. Toward the end of their first year, it appears we are making a positive impact on the majority of these students, whether they were enrolled because of

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Biotech Companies In Good Shape Despite Large Losses in 1991

■ **Stronger product sales, profits for several firms helped drive stock offerings to new highs, building cash reserves for many in 1992**

Ann M. Thayer,
C&EN Northeast News Bureau

Biotechnology companies have started 1992 with large bankrolls from which to fund R&D—despite large losses last year for many companies. This is because 1991 was the most prosperous financing year in the history of the biotechnology industry. Together, companies of every shape and size raised more than \$4 billion through public stock offerings. Investors' overall enthusiasm for biotechnology—which includes a large number of young, unproven companies—was generated by the success of a handful of companies with big products and profits.

In addition, acquisitions of prominent biotechnology companies by large pharmaceutical firms, and by other biotechnology companies, placed tremendous market valuations on these companies despite their histories of problems. Chiron's merger with industry-pioneer Cetus was a major event within the industry for its sheer size at \$650 million and the boldness of a successful, but only marginally profitable, Chiron. Since then, Cetus' key product, interleukin-2, finally received a favorable recommendation from a Food & Drug Administration advisory panel after long delays (C&EN, Jan. 27, page 6).

Genetics Institute, after a setback in a prolonged patent dispute with Amgen, sold a 60% interest to American Home Products for \$660 million. Genetics Institute, which had reported sizable losses over the past few years, has gained a more comfortable cash position to support its promising, albeit long-term,

R&D. In 1991, the company spent 82% of revenues on R&D. It does not expect to be profitable in 1992, since spending on R&D is to be increased significantly.

One of the biggest surprises for the industry came when Sandoz, the Swiss chemicals and pharmaceuticals producer, paid \$392 million for a 60% stake in SyStemix. SyStemix, which is developing therapeutic agents based on immune and blood cell precursors, is only four years old and has no products in clinical trials. The company's stock, which became publicly traded only four months before the acquisition, rose to \$54 per share and more than doubled SyStemix's market value.

Thus, throughout 1991, biotechnology stocks outperformed the stock market as a whole with the market valuation for biotechnology companies reaching more than \$35 billion. The favorable environment for biotechnology stocks led to more than 85 public offerings in 1991, reports Feinstein Partners, a Cambridge, Mass.-based consulting firm. Of these, 35 were initial public offerings of stock. Among the standouts with initial offerings were Regeneron, which raised \$99 million, and Affymax, with \$92 million.

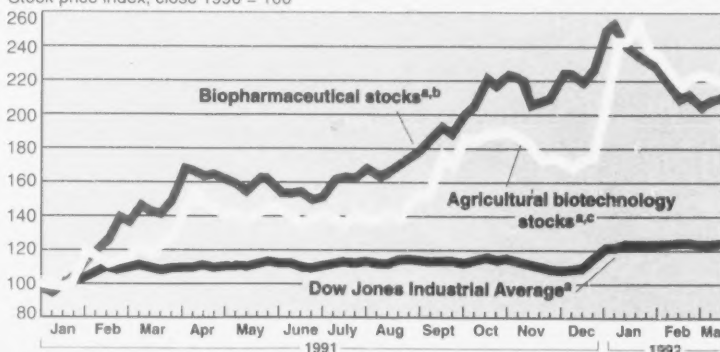
Many others easily raised between \$30 million and \$60 million.

As stock prices continued to rise, at least 12 companies "double-dipped" into the market by following their initial public offering with a secondary stock offering. The results of secondary offerings were dramatic, with Synergen raising \$225 million; Genzyme, \$143 million; Chiron, \$132 million; MedImmune, \$109 million; and Immunex, \$107 million. The performance of stocks after the offerings also was remarkable. Nearly 25 companies saw their stock values at least double, and others, such as MedImmune, saw prices triple or quadruple.

The stock market picture is not without its downside. Following Regeneron's initial public offering in April, its stock value crashed on critical analyst reports. In doing so, it contributed to a less positive outlook on biotechnology stocks overall. As investor interest cooled, the number of stock offerings dropped. This was typical of the continual ups and downs seen throughout the year, which can be attributed to the volatile and event-driven nature of biotechnology stocks.

Biotech stocks outrun stock market index

Stock price index, close 1990 = 100



^a Reindexed to show relative change. Prices as of Friday close each week. ^b Based on stock prices for Amgen, Applied Bioscience, Biogen, Centocor, Chiron, Cytogen, Genentech, Genetics Institute, Immunex, Repligen, and Xoma. ^c Based on stock prices for Calgene, Crop Genetics, DNA Plant Technology, Ecogen, and Mycogen.

However, by late summer and early fall, biotechnology stocks started climbing to a new high and the number of offerings grew once again. But this was followed by a November stock market downturn that hit biotechnology stocks harder than others. Several companies' stock prices, including those of big gainers MedImmune, Immune Response, and Synergen, fell as much as 15 to 20% overnight. Even successful, established companies such as Amgen, Biogen, and Chiron, saw stock prices drop 10%. Although stocks recovered and continued strong for the remainder of 1991 and in early 1992, they have since lost some of the earlier gains through market fluctuations and profit taking.

Those companies that took advantage of the stock market highs with successful stock offerings now have large amounts of cash with which to fund R&D. Companies such as Immune Response, Scios, ImmuLogic, Immunex, Regeneron, and Xoma list nearly \$100 million or more in cash on their balance sheets; a host of others report as much as \$50 million to \$60 million. Despite a cost of \$100 million or more to take a biopharmaceutical product from discovery through development, the money may sustain some companies, depending on their size, stage of development, and ability to manage the money wisely, for a few years. However, at the end of that time, many are expected to once again compete to raise capital.

More established companies, with products in later stages of development, spend a proportionately larger amount on R&D. Amgen spent \$121 million on R&D in 1991, but has \$378 million in cash as a result of its highly profitable business. Similarly, Genentech spent \$221 million, or 43% of revenues, on R&D in 1991, but has \$515 million in cash following its merger with Hoffmann-La Roche. Genentech and Immunex, which are both profitable, plan to increase expenditures to 50% of revenues in 1992. The industry average for R&D spending is about 63% of revenues, but can run as high as 200%, and is many more times that of the pharmaceutical industry average of 10 to 15%.

Chiron spent \$79.4 million on R&D and, despite the cost of acquiring Cetus, has more than \$300 million in cash. This comes in part from Cetus' sale of its polymerase chain reaction technology to Hoffmann-La Roche and the strength of Chiron's ophthalmics and

Biotech companies' losses outweigh profits in 1991

\$ Thousands	Revenues ^a	Earnings	% change from 1990		Profit margin ^b	
			Revenues	Earnings	1991	1990
BIOPHARMACEUTICAL						
Affymax	\$ 4,465	\$ 8,605	312%	nm	def	def
Agouron Pharmaceuticals	4,922	8,008	13	nm	def	def
Amgen	682,043	97,852	128	2432%	14%	1%
Biogen	69,577	7,186	17	7	10	13
BioTechnology General	5,136	7,930	19	nm	def	def
Cambridge Biotech	28,981	348	33	nm	1	def
Cambridge Neuroscience	1,085	-8,736	5	nm	def	def
Centocor	53,197	195,555	18	nm	def	def
Chiron ^c	118,459	425,131	51	nm	def	9
Cor Therapeutics	2,418	5,116	405	nm	def	def
Cytel	7,109	11,999	9	nm	def	def
Cytogen	10,851	15,344	131	nm	def	def
Enzo Biochem	20,279	8,242	-1	nm	def	def
Enzon ^d	4,058	21,510	235	nm	def	def
Genelabs	4,261	22,934	52	nm	def	def
Genentech	515,924	44,322	8	nm	9	def
Genetic Therapy	472	-4,824	167	nm	def	def
Genetics Institute	82,551	10,748	105	nm	def	def
Genzyme	121,706	18,881	122	n/n	16	def
ImClone	800	-7,599	-84	nm	def	def
ImmuLogic	4,604	9,941	-2	nm	def	def
Immune Response	4,253	-3,001	-1	nm	def	def
Immunex	62,615	802	80	nm	1	def
Immunogen	2,137	-12,648	-32	nm	def	def
Immunomedics	8,057	542	83	nm	7	def
Isis Pharmaceuticals	8,043	-8,737	311	nm	def	def
Liposome	8,832	-4,086	25	nm	def	def
MedImmune	13,952	1,624	327	nm	12	def
MGi Pharma	8,657	-8,715	36	nm	def	def
NeoRx	315	-11,651	-82	nm	def	def
Nova Pharmaceuticals	50,094	-14,852	39	nm	def	def
Oncogene Science	8,334	-2,305	36	nm	def	def
Regeneron	12,508	-4,468	149	nm	def	def
Repligen	9,637	-13,426	-10	nm	def	def
Ribi ImmunoChem	1,386	-3,217	5	nm	def	def
Scios ^e	7,357	-17,251	-41	nm	def	def
Synergen	23,822	-7,120	87	nm	def	def
T Cell Sciences	10,548	-4,093	-12	nm	def	def
Xoma	17,140	-34,342	16	nm	def	def
AGRICULTURAL						
Calgene ^f	8,001	8,783	0	nm	def	def
Crop Genetics	3,344	8,386	13	nm	def	def
DNA Plant Technology	10,302	14,941	19	nm	def	def
Ecogen	6,940	10,529	217	nm	def	def
Mycogen	23,642	3,305	58	nm	def	def
OTHER						
Applied Bioscience	113,779	12,473	14	53	11	8
Collagen	62,617	7,852	7	nm	def	6
Immucor	25,079	3,431	68	37	14	17

a. Includes product sales, contract research, royalty, and interest revenues for calendar year. b. After-tax income as percentage of sales. c. Acquired Cetus in December, 1991. Loss includes one-time charge of \$426 million. d. Acquired Genex in June 1991. e. Name changed in early 1990; previously known as California Biotechnology. f. Results reported converted from 1991 only because of change in fiscal year. def: deficit; nm: not meaningful.

Companies' major products rack up huge sales

Company	Products	1991 sales (\$ million)	% change from 1990
Amgen	Erythropoietin and granulocyte colony-stimulating factor	\$645.3	129%
Biogen	α -, β -, and γ -interferons; hepatitis B vaccines and diagnostics	56.5 ^a	26
Centocor	Antisepsis monoclonal antibody; cancer diagnostics	44.3 ^b	35
Chiron	Diagnostics and ophthalmics	28.2 ^c	91
Genentech ^d	Human growth hormone	185.1	18
	Tissue plasminogen activator	196.5	6
	γ -interferon	1.5	nm
Genetics Institute	Erythropoietin	18.4 ^e	124
Genzyme	Glucocerebrosidase	81.1	134
Immunex	Granulocyte macrophage colony stimulating factor	34.2	601

^a Predominantly royalty income from sales by licensees. Actual sales estimated to be several hundred million dollars.
^b European sales. ^c Does not include revenues from sales by joint businesses. ^d Does not include royalty income from licensees' sales of human albumin and γ -interferon. ^e Royalty income on sales by European and Japanese partners. nm: not meaningful.

diagnostics businesses. Similarly, based on the strength of its royalty income from products it has developed and a \$74 million stock offering, Biogen has the cash to back its more than \$40 million R&D program.

Although large companies spend more, they are more likely to have other sources of revenue and thus their survival rates are slightly higher than for small companies. Most biotechnology company revenue comes not from earnings, but rather from collaborative R&D arrangements, interest income, and private investments. But for companies with products, such as Amgen, Genentech, Genzyme, and Immunex, sales of a major product can be substantial.

Combined sales of these companies' products—seven of the 14 approved to date by FDA—totaled more than \$1.1 billion in 1991. Amgen's red blood cell stimulant, erythropoietin, became the top-selling product for a biotechnology company. Amgen's revenues of \$682 million and a net income of \$97.9 million made it the leading biotechnology company. Genentech's human growth hormone showed increased sales, but its tissue plasminogen activator lost ground because of strong competition from less expensive drugs. Net income for the company was \$44.3 million on revenues of \$516 million.

Colony-stimulating factors are just beginning to show their potential, having first been approved in 1991, and have contributed to product sales for Immunex and Amgen. Biogen's \$57 million in royalties, meanwhile, are only a small

reflection of the magnitude of licensees' sales of α -interferon and hepatitis B vaccines and diagnostics. And, at \$81 million in sales in just about eight months on the market, Genzyme's enzyme therapeutic product, Ceredase, contributed to two thirds of that company's \$122 million in revenue. Genzyme had a net income of \$18.9 million in 1991.

Speculation that products might soon emerge from among the 100-plus biotechnology drugs in clinical trials and more than 20 awaiting FDA approval keeps the excitement level high. Monoclonal-antibody-based therapeutics and imaging agents, blood clotting factors, and interleukin-2 are anticipated to be the next products to receive marketing approval. Expanded uses for approved products such as the colony-stimulating factor and interferons also are expected to get marketing okay. Still, only a handful of biotechnology companies are profitable and more companies continued to lose money than make it in 1991.

The biggest losses were reported by companies that had been investing heavily in R&D, product development, and setting up manufacturing and marketing efforts. Chiron's acquisition of Cetus cost the company a \$426 million charge against earnings in 1991 for a net loss of \$425 million after having reported a profit in 1990. In 1991, the company had revenues of \$118 million and anticipates returning to profitability in 1993.

Centocor reported a \$196 million loss on revenues of \$53 million for 1991. The loss was due in part to a \$70 mil-

lion charge for acquired research. The company has been expanding its sales and marketing efforts in Europe where its monoclonal antibody product, Centoxin, has been approved for treating sepsis. The company is involved in fierce competition and patent disputes with Xoma, although both companies' products have faced delays at FDA.

A side of the industry that has generated less excitement is agricultural biotechnology. Even so, this area of development also is showing gradual progress and growth by the companies involved. Although none of the five companies followed in the C&EN agricultural biotechnology stock index—Calgene, Crop Genetics, DNA Plant Technology, Ecogen, and Mycogen—reported a profit for 1991, they have strengthened their financial and product development positions.

In 1991, EPA approved the first two genetically engineered biopesticides developed by Mycogen for commercial sale. Although product sales are still low and money was spent on acquiring new technology, the company has managed to increase its cash balance to about \$76 million through a stock offering.

Calgene refocused its business last year and anticipates commercial developments for its genetically engineered crops. DNA Plant Technology is using proceeds from its October 1991 offering to expand development of its core businesses. For Crop Genetics, a major event in 1991 was the signing of its first large collaborative agreement with Du Pont.

In 1991, Ecogen saw revenues more than triple over 1990. New alliances, new technology, and increased assets contributed to a major comeback in the value of the company's stock, increasing fivefold over the start of 1991 and remaining strong in 1992.

Whereas the excitement toward biotechnology permeated the entire industry in 1991, most observers do not expect this to continue and anticipate that high-priced biotechnology stocks are susceptible to a fall. A major uncertainty hanging over individual companies' success is the lengthy, expensive, and uncertain product development and regulatory approval processes. Unless more than the handful of biotechnology companies showing profits can deliver high-quality science, real products, and profits, the opportunity for raising capital will fade. □

Because very little combustible liquid material is in the reactor at any time, the gas-phase processes are inherently safer than other types. Slurry processes, for example, involve great volumes of solvents.

Moreover, the gas-phase processes, because they do not require steam or solvents, involve only polymerization and pelleting equipment. This simpler approach can reduce construction costs up to 30% over conventional slurry processes of similar capacity, Brockmeier says. Operating costs also are lower, he says, as much as 35% less than for slurry processes, excluding monomer costs.

The major differences between the three major gas-phase processes involve heat removal and agitation. The BASF/ICI/Norchem and Amoco/Chisso processes use mechanical agitation, whereas the Union Carbide/Shell process uses a fluid bed, which is also an efficient remover. The BASF/ICI/Norchem and Amoco/Chisso processes depend on the latent heat of vaporization of propylene as a heat sink.

The Amoco/Chisso process consists of several major steps. First is monomer purification. Monomers must be very pure, with such catalyst poisons as moisture, sulfur compounds, and oxygen reduced to concentrations of less than 1 ppm. The simplest part of the process, according to Brockmeier, is handling the catalyst: catalyst, cocatalyst, and modifiers are fed to the reactor, through appropriate meters, directly from the shipping containers.

The distinctive feature of the Amoco/Chisso process is the reactor, Brockmeier says. Catalyst is injected at one end of the reactor, and product is removed from the other end. The residence time distribution in the reactor resembles that of plug-flow in a tubular reactor. This allows quick transitions from one product grade to another as well as between homopolymers and copolymers. Process shutdowns from fouling are not required, he says, and startup is easy, even if the reactor has been exposed to the atmosphere.

The heat of polymerization is removed by vaporizing condensed recycle monomer that is sprayed on the stirred powder bed. The evaporated monomer leaving the reactor is partially condensed and recirculated for cooling. Makeup monomer is added to the recycle as needed.

In homopolymer production, propylene is the only monomer fed to the system. For random copolymer production, a controlled amount of ethylene is added. Impact copolymer production requires addition of a second reactor, similar to the first, with a gas lock between them.

The reactor/catalyst system is stable enough for the process to be stopped simply by halting flow of the catalyst to the reactor, Brockmeier says. In an emergency, the process can be shut down within three minutes by venting pressure to the flare system. It can be restarted by repressurizing the system back to the operating pressure.

The powdered product from the final reactor is periodically discharged into a separation system, where excess monomer is removed for recycling and a countercurrent gas stream deactivates

the catalyst. The deactivated product is then mixed with stabilizers. Pelleting is done with water. After dewatering, the product is sent to storage. Except for the product itself and a small gas stream that is flared to the atmosphere, no effluents result from the process.

The demand for polyethylene and polypropylene products continues to grow. It's estimated that world demand will grow 5% per year through the 1990s and that world production of these products will be about 10 million tons per year in the near future. The most promising locations for expanding production in polyethylene/polypropylene products at present are Southeast Asia, the Middle East, and Latin America. The developed countries will continue to expand production at a slower rate.

Joseph Haggin

Size of U.S. biochemistry departments surveyed

The University of California, Davis, has the largest undergraduate department of biochemistry in the U.S., with 575 undergraduates, according to a survey conducted last year by the biochemistry department at North Carolina State University, Raleigh. The survey covers 1990 data from departments at 98 universities.

Paul F. Agris, head of NC State's department of biochemistry, says he's not aware of any other survey of the size of undergraduate biochemistry degree programs in at least a decade. NC State, which ranked second in the survey, had 245 undergraduates in 1990. However, the department has been growing fantastically, Agris says, and now has more than 320 majors and comajors. Many of the students, he points out, double major in either chemistry or chemical engineering. A survey of NC State graduates, he adds, has shown that about 50% enter graduate schools. Of the other 50%, most find jobs in technical fields in industry or academic and medical institutions, with a few going into sales.

Among the data gathered in the survey were level of degrees in biochemistry, number of faculty members, number of students majoring in biochemistry, number of foreign versus U.S. students, and course information such as size of lecture classes, number of staff in the department, and some budgetary information. In reporting data

Of undergraduate biochemistry programs, UC-Davis is largest

University	Number of undergraduates	Number of biochemistry faculty ^a
University of California, Davis	575	18
North Carolina State University	245	12
Virginia Polytechnic Institute & State University	240	20
University of Wisconsin, Madison	217	29
Northwestern University	200	32
University of California, Riverside	185	15
Michigan State University	174	36
University of Arizona, Tucson	168	48
University of Missouri, Columbia	150	30
Pennsylvania State University	119	27

Note: Data are for 1990. ^a Full-time equivalent faculty. Source: North Carolina State University survey of biochemistry degree programs in the U.S., 1990-1991.

for comparison, the survey sponsors averaged data for most categories and selected certain institutions to represent the three subgroups of public, private, and public southeastern institutions.

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